PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

X16541

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

20 SEP 2005

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/037181	16.11.2004	20.11.2003

International Patent Classification (IPC) or both national classification and IPC
C07D333/70, C07D333/68, A61K31/559, A61P3/14

Applicant
ELI LILLY AND COMPANY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/037181

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 20-25

because:

☒ the said international application, or the said claims Nos. 20-25 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-30
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-30
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-19,26-30
	No:	Claims	20-25

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/US2004/037181

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 20 to 25 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: CARSTEN CARLBERG & ANTONIO MOURINO: EXPERT OPINION, vol. 13, no. 6, 2003, pages 761-772, XP002331659

D2: US-B1-6 531 459 (STEINMEYER ANDREAS ET AL) 11 March 2003 (2003-03-11)

D3: WO 03/101978 A (ELI LILLY AND COMPANY; DAHNKE, KARL, ROBERT; GAJEWSKI, ROBERT, PETER;) 11 December 2003 (2003-12-11)

Novelty

The present application refers to three compound-claims (1 to 3, each of them independently formulated) which are characterized by the presence of
i) a benzo[b]thiophene ring and
ii) a 4-substituted phenyl-alkylene chain attached at i)
Pharmaceutical formulations comprising those compound(s) are also claimed.

None of the document cited shows the relevant hetero bicyclic ring whereas the substitution pattern has been already described for synthetic analogues of the biologically active form of vitamin D, namely vitamin D_3.
D1 is a comprehensive review regarding the patent literature on $1\alpha,25\text{-}(OH)_2\text{-}D_3$ analogues described in the last years with promising selective profiles which, indeed, never show the benzo[b]thiophene ring.

Novelty can be thus recognized.

Inventive step

The problem underlying the present application appears to reside in the provision of alternative or improved pharmaceutical agents that mimic 1α,25-dihydroxyvitamin D_3 to stimulate i.a. bone formation or restore bone quality without the disadvantage of hypercalcemia.
The solution resides in the provision of compounds having a nucleus of three different Formulas (see as on page 3), the VDR modulating agents being represented by formulae (IA) to (IC).
Data are given as from page 157 in terms of EC_{50} values according to the summary of experimental results. Control experiments are done with compounds including calcipotriol and the other known VRD ligands also described in D1 and D2 (see present pages 161 and 162 for the structural formulas).
The quantitative data including the comparison with compounds from the closest prior art show that the problem has been solved.

"Prodrug"- Protection cannot be sought for speculative compounds, which have yet to be prepared and investigated. There is no specific indication within the application as to what may be a prodrug, nor is a prodrug a definable term as regards the structure of such a compound. The skilled person has no indication as to what falls within this definition, and it should thus be deleted.

Industrial applicability
For the assessment of the present claims 20 to 25 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI
Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
PCT/US03/14539	11.12.2003	22.05.2003	29.05.2002

Re Item VIII

Certain observations on the international application

Also in view of the prior art acknowledged by the Applicant it is not clear why it was necessary for him to include a proviso in Claim 1. If this proviso has been inserted because the compounds thus excluded do not possess the desired pharmacological properties, this should be made clear in the reply to this communication. However if this proviso is directed at the exclusion of specific compounds known to the Applicant, the relevant prior art should be incorporated in the description (cf. Rule 5.1(a) and if said prior art was published before the relevant priority dates of the present application and relates to compounds having a similar utility to the compounds of the present application, it will also be necessary to show that the compounds claimed solved the problem as stated above vis-à-vis these compounds.